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<p>(54) Title: SPONTANEOUSLY DISPERSIBLE N-BENZOYL STAUROSPORINE COMPOSITIONS</p> <p>(57) Abstract</p> <p>Spontaneously dispersible N-benzoyl-staurosporine compositions are discussed for oral administration having high bioavailability levels and reduced variability of bioavailability levels of N-benzoyl-staurosporine, as well as their preparation and use in medical treatment.</p>			

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SPONTANEOUSLY DISPERSIBLE N-BENZOYL STAURUSPORINE COMPOSITIONS

The present invention relates to novel pharmaceutical compositions in which an active agent
5 is N-benzoyl-staurosporine as disclosed e.g. in US 5,093,330 and equivalents thereof.

US 5,093,330 specifically discloses two tablet formulations based on starch/lactose mixtures in the presence of colloidal silica, talc and magnesium stearate (Examples 52 and 53) and a capsule formulation based on talc and colloidal silica (Example 54). We have
10 found that N-benzoyl-staurosporine presents highly specific difficulties in relation to administration generally and pharmaceutical compositions in particular, including problems with drug bioavailability and variability in inter- and intra-patient dose response, e.g. with respect to US 5,093,330. We have found it to be very lipophilic and practically insoluble in water, in simulated gastric and in intestinal fluids (solubility <0.1 mg/L). In particular this
15 exceptional low solubility of the active substance necessitated development of a non-conventional dosage form.

In accordance with the present invention it has now surprisingly been found that stable pharmaceutical compositions with N-benzoyl-staurosporine having particularly interesting
20 bioavailability characteristics and reduced variability in inter- and intra-subject bioavailability parameters, e.g. with respect to US 5,093,330, are obtainable. These novel N-benzoyl-staurosporine compositions have been found to meet or substantially reduce the difficulties encountered previously. It has been shown that the compositions in accordance with the present invention may enable effective N-benzoyl-staurosporine dosaging with
25 concomitant enhancement as well as reduced variability of resorption/bioavailability levels for and between individual patients. Such reductions in variability in in inter- and intra-subject bioavailability may be particularly found with respect to the specific formulations described. More particularly, it has been found that these compositions may contain solubilized N-benzoyl-staurosporine in sufficiently high concentration to permit
30 convenient oral administration without exhibiting precipitation of the active agent. Thus, the invention may achieve effective therapy with lower N-benzoyl-staurosporine dosage levels and may permit closer standardization and optimization of daily dosage requirements for

each individual. Consequently, occurrence of undesirable side-effects is diminished and overall cost of therapy may be reduced.

In one aspect the present invention provides a pharmaceutical composition for oral
5 administration comprising N-benzoylstaurosporine having a high level of bioavailability, e.g. as determined by measuring plasma concentrations over time, as defined by the Area Under the Curve (AUC) in units of mass-time/volume.

In another aspect the present invention provides a pharmaceutical composition for oral
10 administration comprising N-benzoylstaurosporine having a reduced variability of bioavailability. In preferred embodiments variability of bioavailability is reduced by providing N-benzoylstaurosporine in form of a spontaneously dispersible pharmaceutical composition.

15 In another aspect the present invention provides a spontaneously dispersible pharmaceutical composition for enteral, e.g. oral, administration comprising N-benzoyl-staurosporine, for example in the form of a micellar precursor.

The term spontaneously dispersible pharmaceutical composition as used herein is defined as
20 a system that is capable of producing colloidal structures, e.g. colloids or analogous structures, e.g. droplets, particles, micelles, e.g. swollen micelles, microemulsions and/or aggregates, of e.g. up to 1000 nm, e.g generally more than 5 nm, when diluted with an aqueous medium. Such systems may be defined as consisting of one component or phase (the dispersed component or phase) finely divided and distributed throughout a second
25 component or phase (the dispersion medium or continuous component or phase), e.g. systems ranging from molecularly dispersed solutions wherein the mean size of the dispersed component or phase may be e.g. less than 200 nm, e.g. more than 5 nm, to macroemulsions wherein the mean size of the dispersed component or phase may be of e.g. up to 1000 nm, e.g. more than 200 nm. The aqueous medium may be for example water,
30 for example on dilution of e.g. 1:10, or gastric juices, e.g. simulated conditions after oral application. The colloidal structures, e.g. colloids or analogous structures, e.g. droplets, particles and/or micelles, are formed spontaneously or substantially spontaneously when the

components of the dispersible pharmaceutical composition are brought into contact with an aqueous medium, e.g. by simple shaking by hand for a short period of time, for example for 10 seconds. Such spontaneously dispersible pharmaceutical compositions are thermodynamically stable, e.g. from at least 15 minutes or 4 hours to 24 hours. Typically, 5 they contain dispersed, e.g. colloidal structures, e.g. colloids or analogous structures, of a size less than about 200 nm as measured by standard light scattering techniques, e.g. using a Malvern Zetasizer 3000, preferably they comprise droplets or particles having a mean diameter of less than about 150 nm, typically less than 100 nm, generally greater than 5 nm. The micellar compositions or the micellar part of such spontaneously dispersible 10 compositions may be monophasic and substantially non-opaque, i.e. transparent or opalescent when viewed by optical microscopic means.

Alternatively, the spontaneously dispersible pharmaceutical composition may form simultaneously a mixture comprising aqueous micelles and nanoparticles. Such 15 nanoparticles may have a particle size of from 150 nm to about 1000 nm, generally in the range of 200 to 800 nm. It was found that the amount of nanoparticles produced may be temperature dependent but still adequate bioavailability characteristics may be obtained.

Although the invention has been described particularly with respect to a spontaneously 20 dispersible pharmaceutical composition a man skilled in the art will appreciate that other systems may be prepared.

In another aspect the present invention provides a spontaneously dispersible pharmaceutical composition for oral administration comprising

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- 1) N-benzoyl-staurosporine,
- 2) a hydrophilic component, and
- 3) a surfactant.

30 In yet another aspect the invention provides a method of increasing bioavailability of N-benzoylstaurosporine by mixing N-benzoylstaurosporine with a carrier comprising a hydrophilic component, and a surfactant.

In another aspect the present invention provides a pharmaceutical composition for increasing the bioavailability of N-benzoylstaurosporine which comprises

- 1) N-benzoyl-staurosporine,
- 5 2) a hydrophilic component, and
- 2) a surfactant.

The spontaneously dispersible pharmaceutical composition (hereinafter embraced by the term pharmaceutical composition of the present invention) is preferably in the form of a 10 colloidal structures, e.g. colloids or analogous structures, e.g. a micellar precursor. N-benzoyl-staurosporine is hereinafter also referred to as the active agent and all other components of the spontaneously dispersible pharmaceutical composition may be hereinafter referred to as the carrier of the spontaneously dispersible pharmaceutical composition. The components of the spontaneously dispersible pharmaceutical 15 compositions may be described in Fiedler, H. P. "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", Editio Cantor, D-7960 Aulendorf, 4th revised and expanded edition (1996), the contents of which are hereby incorporated by reference.

In accordance with the present invention N-benzoyl-staurosporine may be present in an 20 amount by weight of up to about 20% by weight of the composition. Preferably the active agent is present in an amount of 1 to 15% by weight of the composition, for example about 5 to 10%, and more preferred 5%.

The hydrophilic component preferably provides for fast mixing of the active agent with 25 water on admixture with water and may be determined by routine experimentation, for example by various chromatography methods, e.g. Gas Chromatography (GC). The hydrophilic component may comprise a main or sole component, e.g. an alcohol, e.g. ethanol, or alternatively may comprise a co-component which may be selected from partial ethers or lower alkanols. Preferred lower alkanol components include ethanol, 1,2-30 propylene glycol or a polyethylene glycol, e.g. of a molecular weight of 100 to 600 daltons, e.g. polyethylene glycol 400. When present in the invention ethanol may comprise up to 60 % by weight of the hydrophilic component; preferably 20 to about 55% by weight, more

preferably about 25 to about 40 % by weight. Especially preferred partial ethers are those known and commercially available as for example glycofurool (also known as tetrahydrofurfuryl alcohol polyethylene glycol ether). These co-components when present are e.g. a partial replacement of other components of the hydrophilic component such that

5 the efficacy of the hydrophilic component as part of the N-benzoyl-staurosporine carrier is not materially impaired. The hydrophilic component may further comprise triethylcitrate, Transcutol, N-methylpyrrolidone, dimethylisosorbide, or propylene carbonate.

The total amount of the hydrophilic component present in the spontaneously dispersible

10 pharmaceutical compositions of the present invention may comprise 5 to 50% by weight of the carrier, e.g. 10 to 50%; preferably 10 to 40% by weight, more preferably about 15 to 35 % by weight.

Pharmaceutical compositions of the present invention further comprise at least one

15 pharmaceutically acceptable surfactant. Surfactants useful for the present invention may be of the anionic, cationic, amphoteric or non-ionic type or mixtures thereof and have generally a hydrophilic-lipophilic balance (HLB) value of from about 3 to 20. Usually nonionic surfactants are preferred, particularly those non-ionic surfactants that have an HLB value of greater than 10, e.g. 14 to 20. Alternatively, the pharmaceutical

20 compositions of the present invention may embrace systems comprising a mixture of surfactants, e.g. a mixture of a first surfactant and one or more co-surfactants selected from any of the surfactant types listed below. Especially preferred are specific combinations of a surfactant having a high HLB value with a co-surfactant having a low HLB value, for example a combination of a polyoxyethylene castor oil derivative, e.g. Cremophor RH 40

25 (HLB 14-16) and a transesterified ethoxylated vegetable oil, e.g. Labrafil M2125 CS (HLB 3-4).

Particularly preferred surfactants of high HLB value, e.g. HLB > 10, are the following:

30 (i) Reaction products of a natural or hydrogenated vegetable oil and ethylene oxide, i.e. polyoxyethylene glycolated natural or hydrogenated vegetable oils, for example polyoxyethylene glycolated natural or hydrogenated castor oils. The natural or

hydrogenated castor oil may be reacted with ethylene oxide in a molar ratio of from about 1:35 to about 1:60, with optional removal of the polyethyleneglycol component from the products. Various of such surfactants are commercially available. The polyethyleneglycol hydrogenated castor oils available under the trade name

5 CREMOPHOR are especially suitable (Fiedler, loc. cit., 1, p. 392-395). Particularly suitable are CREMOPHOR RH 40, which has a saponification number of about 50 to 60, an acid number less than about 1, a water content (Fischer) less than about 2%, an n_D^{20} of about 1.453 to 1.457 and an HLB of about 14 to 16; and CREMOPHOR RH 60, which has a saponification number of about 40 to 50, an acid number less than
10 about 1, an iodine number of less than about 1, a water content (Fischer) of about 4.5 to 5.5%, an n_D^{25} of about 1.453 to 1.457 and an HLB of about 15 to 17. An especially preferred product of this class is CREMOPHOR RH40. Also suitable are polyethyleneglycol castor oils such as that available under the trade name
15 CREMOPHOR EL, which has a molecular weight (by steam osmometry) of about 1630, a saponification number of about 65 to 70, an acid number of about 2, an iodine number of about 28 to 32 and an n_D^{25} of about 1.471 and an HLB value of about 12 to 14. Also suitable are the various tensides available under the trade names NIKKOL
20 (e.g. NIKKOL HCO-40 and HCO-60), MAPEG (e.g. MAPEG CO-40h), INCROCAS (e.g. INCROCAS 40), and TAGAT, for example polyoxyethylene-glycerol-fatty acid esters, e.g. TAGAT RH 40, and polyoxyethylene-glycerol-trioleates, e.g. TAGAT TO having a HLB value of 11.3. These surfactants are further described in Fiedler loc. cit..

25 (ii) Related products that belong to the class of polyoxyethylene alkyl ethers are available under the tradename BRIJ, e.g. Brij 35 which has an HLB value of about 16.9.

(iii) Polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters of the type known and commercially available under the trade name MYRJ (Fiedler, loc. cit., 2, p.1042-1043). An especially preferred product of this class is MYRJ 52 having a n_D^{25} of about 1.1, a melting point of about 40 to 44°C, an HLB value of about 16.9,
30 an acid value of about 0 to 1 and a saponification no. of about 25 to 35. Other related products include polyethoxylated saturated hydroxy fatty acids which may be produced

by reacting a saturated hydroxy fatty acid, e.g. C₁₈ to C₂₀ with e.g. ethylene oxide or polyethylene glycol. Suitable examples for the present invention include are known and commercially available, e.g. from the BASF company under the trade mark Solutol. Especially preferred is Solutol HS15 which is known, e.g. from the BASF technical leaflet MEF 151E (1986), to comprise of about 70% polyethoxylated 12-hydroxystearate by weight and about 30% by weight unesterified polyethylene glycol component. Solutol HS 15 has a hydrogenation value of 90 to 110, a saponification value of 53 to 63, an acid number of maximum 1, and a maximum water content of 0.5% by weight.

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(iv) Polyoxyethylene-sorbitan-fatty acid esters (also called polysorbates), for example mono- and tri-lauryl, palmityl, stearyl and oleyl esters of the type known and commercially available under the trade name TWEEN (Fiedler, *loc. cit.*, 2, p.1615-1619) including the products TWEEN

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20 [polyoxyethylene(20)sorbitanmonolaurate] with an HLB of about 16.7,
21 [polyoxyethylene(4)sorbitanmonolaurate] with an HLB of about 13.3,
40 [polyoxyethylene(20)sorbitanmonopalmitate] with an HLB of about 15.6,
60 [polyoxyethylene(20)sorbitanmonostearate] with an HLB of about 14.9,
65 [polyoxyethylene(20)sorbitantristearate] with an HLB of about 10.5,
20 80 [polyoxyethylene(20)sorbitanmonooleate] with an HLB of about 15.0,
81 [polyoxyethylene(5)sorbitanmonooleate] with an HLB of about 10.0,
85 [polyoxyethylene(20)sorbitantrioleate] with an HLB of about 11.0.
Especially preferred products of this class are TWEEN 40 and TWEEN 80.

25 (v) Hydrophilic tocopherol esters, e.g. d-alpha-tocopheryl polyethylene glycol 1000 succinate.

30 (vi) Polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, for example of the type known and commercially available under the trade names PLURONIC, EMKALYX and POLOXAMER (Fiedler, *loc. cit.*, 2, p. 1198-1204). An especially preferred product of this class is PLURONIC F68, having a melting point of about

52°C and a molecular weight of about 6800 to 8975. A further preferred product of this class is POLOXAMER 188, which has an HLB value of about 29.

Particularly preferred co-surfactants having a low HLB value, e.g. HLB < 10, are the
5 following:

- (i) Sorbitan fatty acid esters, e.g. of the type known and commercially available under the trade name Span, for example including sorbitan-monolaureyl ester (HLB 8.6), -monopalmityl ester (HLB 6.7), -monostearyl ester (HLB 4.7), -tristearyl ester (HLB 10 2.1), -monooleyl ester (HLB 4.3), and -trioleyl esters (HLB 1.8) (Fiedler, loc. cit., 2, p. 1430).
- (ii) Propylene glycol mono- and di-fatty acid esters such as propylene glycol dicaprylate (also known and commercially available under the trade name MIGLYOL 840), propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate and so forth (Fiedler, loc. cit., 2, p. 1008-1010). Propylene glycol mono C₈ esters include Sefsol 218 (Nikko Chemicals) and Capryol 90 (Gattefossé).
- (iii) Transesterified ethoxylated vegetable oils such as those obtained by reacting various natural vegetable oils (for example, maize oil, kernel oil, almond oil, ground nut oil, olive oil, soybean oil, sunflower oil, safflower oil and palm oil, or mixtures thereof) with polyethylene glycols that have an average molecular weight of from 200 to 800, in the presence of an appropriate catalyst (according to known procedures described in 20 the literature, e.g. US Patent 3 288 824). Transesterified ethoxylated corn oil is particularly preferred. Various forms of transesterified ethoxylated vegetable oils are known and commercially available under the trade name LABRAFIL (Fiedler, loc. cit., 2, p. 880). Especially suitable examples are LABRAFIL M 2125 CS (obtained from 25 corn oil and having an acid number of less than about 2, a saponification number of 155 to 175, an HLB value of 3 to 4, and an iodine number of 90 to 110), and LABRAFIL M 1944 CS (obtained from kernel oil and having an acid number of about 2, a 30

saponification number of 145 to 175 and an iodine number of 60 to 90). LABRAFIL M 2130 CS (which is a transesterification product of a C₁₂₋₁₈ glyceride and polyethylene glycol and which has a melting point of about 35 to 40°C, an acid number of less than about 2, a saponification number of 185 to 200 and an iodine number of 5 less than about 3) may also be used. The preferred transesterified ethoxylated vegetable oil is LABRAFIL M 2125 CS which can be obtained, for example, from Gattefossé, Saint-Priest Cedex, France.

(iv) Mono-, di-and mono/diglycerides, e.g. C₈ to C₁₀ fatty acid mono- and di-glycerides 10 include Capmul MCM, Akoline MCM (from the Karlshamns company), Imwitor 308 and Imwitor 988, which have an HLB value of about 3.8 (from the Contensio company), and especially esterification products of caprylic or capric acid with glycerol. Preferred products are of this class are e.g. those comprising or essentially 15 consisting of caprylic/capric acid mono- and di-glycerides. C₈ to C₁₀ mono-, di-glycerides having 6 to 10 mol-% polyoxyethylene groups, e.g. Softigen 767 (available from Contensio Chemicals). Monoglycerides, e.g. monooleate, glycerol monopalmitate and glycerol monostearate, for example as known and commercially available under the trade names Myvatex, Myvaplex, and Myverol (Fiedler, loc. cit., 2, p. 1044) and acetylated, e.g. mono- and di-acetylated monoglycerides, for example as known under 20 the trade name Myvacet (Fiedler, loc. cit., 2, p. 1043).

(v) Pentaerythriol fatty acid esters and polyalkylene glycol ethers and polyalkylene glycol ethers, for example pentaerythrite-dioleate, -distearate, -monolaurate, -polyglycol ether, and -monostearate as well as pentaerythrite-fatty acid esters (Fiedler, loc. cit., 2, 25 p. 1158-1160)

(vi) Other suitable surfactants include glycerol triacetate or (1,2,3)-triacetin (Fiedler, loc. cit., 2, p. 1580); and sterols and derivatives thereof.

30 Further ionic surfactant classes not represented by the categories described above include

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- (i) Docusate salts, for example dioctylsulfosuccinate or related compounds, for example di-[2-ethylhexyl]-succinate (Fiedler, loc. cit., 1, p. 500).
- 5 (ii) Phospholipids, in particular lecithins (Fiedler, loc. cit., 2, p. 910-912). Lecithins suitable for use in the compositions of the invention include, in particular, soya bean lecithins.

Thus, in another aspect the present invention provides a spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine and a surfactant selected from the group consisting of polyoxyethylenes, for example a 10 polyoxyethylene castor oil, e.g. Cremophor RH40, a polyoxyethylene alkyl ether, e.g. Brij 35, polyglycerols and related polyols, for example a polysorbate, e.g. Tween 20, and polyalkylene oxide copolymers, e.g. Pluronic.

Furthermore, in yet another aspect the present invention provides a spontaneously 15 dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine and a surfactant having a high HLB value of greater than 10, for example selected from the group consisting of a polyoxyethylene castor oil, e.g. Cremophor RH 40, a polyoxyethylene alkyl ether, e.g. Brij 35, and a polysorbate, e.g. Tween 20, and co- 20 surfactant having a low HLB value of less than 10, for example a transesterified ethoxylated vegetable oil, e.g. Labrafil M2125 CS.

Such spontaneously dispersible pharmaceutical composition may be formulated in a conventional manner and may preferably be in a form of a micellar precursor as described above.

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The total amount of surfactant and co-surfactant present in the pharmaceutical composition of the present invention may comprise 5 to 80 % by weight of the carrier; preferably 10 to 70 % by weight, more preferably 20 to 60 % by weight and even more preferably between about 30 % and 55% by weight.

30

The pharmaceutical compositions of the present invention may further comprise a lipophilic component. These compositions may be capable of producing emulsions and related

systems, e.g. microemulsions, e.g. a system with a mean particle diameter of e.g. from 5 nm to 200 nm, e.g. from 5 nm to 100 nm, e.g. aqueous or oily microemulsions, preferably an aqueous microemulsion, upon mixing with an aqueous medium. Preferably the lipophilic component may be characterized by a low HLB value of less than 10, e.g. up to 8.

5 The lipophilic component may comprise fatty acid triglycerides, preferably medium chain fatty acid triglycerides. Especially suitable medium chain fatty acid triglycerides are neutral oils, e.g. neutral plant oils, in particular fractionated coconut oils, for example those known and commercially available under the trade names Captex, Myritol, Capmul, Neobee and Mazol; Miglyol 812 being the most preferred. Miglyol 812 is a fractionated coconut oil comprising

10 caprylic-capric acid triglycerides and having a molecular weight = about 520 daltons. Fatty acid composition = C₆ max. about 3%, C₈ about 50 to 65%, C₁₀ about 30 to 45%, C₁₂ max 5%; acid no. = about 0.1; saponification no. about 330 to 345; iodine no. = max 1. Miglyol 812 is available from the Hüls company. Other suitable triglycerides preferably comprise mixtures of C₈₋₁₀ or C₁₂₋₂₀ fatty acid triglycerides, especially C₁₆₋₁₈ fatty acid triglycerides.

15 The fatty acid component of the triglycerides may comprise both saturated and unsaturated fatty acid residues. Preferably however they are predominantly comprised of unsaturated fatty acid residues; in particular C₁₈ unsaturated fatty acid residues. Suitably the triglycerides comprise at least 60%, preferably at least 75%, more preferably at least 85% by weight of a C₁₈ unsaturated fatty acid (for example linolenic, linoleic and oleic acid)

20 triglycerides. Suitably the triglycerides comprise less than 20%, for example about 15% or 10% by weight or less, saturated fatty acid (for example palmitic and stearic acid) triglycerides.

The lipophilic component may also comprise a transesterification product, generally

25 obtained as described in GB 2 257 359 or WO 94/09211, the contents of which are incorporated herein by reference. Other particularly suitable triglycerides are the purified transesterification products of corn oil and glycerol, hereinafter referred to as corn oil glycerides and produced according to the description of GB 2 257 359 or WO 94/09211.

30 Thus, in another aspect, the invention provides a spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine and a surfactant having a HLB value of greater than 10 and a fatty acid glyceride as a lipophilic component.

The total amount of lipophilic component when present in the spontaneously dispersible pharmaceutical compositions may comprise 5 to 85 % by weight of the carrier, e.g. 10 to 85%; preferably 15 to 70 % by weight, more preferably about 20 to about 50 % by weight.

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Accordingly, in yet another aspect the present invention provides a spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, a surfactant selected from the group consisting of a polyoxyethylene castor oil, e.g. Cremophor RH 40, a polyoxyethylene alkyl ether, e.g. Brij 35, and a polysorbate, 10 e.g. Tween 20, and a lipophilic component selected from the group consisting of a fatty acid glycerides, for example a fractionated coconut oil, e.g. Miglyol 810 and 812, a corn oil glyceride, and a acetylated mono- or diglyceride, respectively.

Such spontaneously dispersible pharmaceutical composition may be formulated in a 15 conventional manner and may preferably be in a form of a micellar precursor as described above.

Where desired, the pharmaceutical compositions of the present invention may comprise further additives or ingredients, for example thickening agents, suspending agents, 20 solidifying agents, as well as antioxidants, e.g. tocopherols, ascorbyl palmitate, butyl hydroxy anisole (BHA), butyl hydroxy toluene (BHT), antimicrobial agents, enzyme inhibitors, stabilizers, preserving agents, and the like. The total amount of these additives or ingredients when present in the invention may comprise about 0.05 to 5 %, preferably 0.1 to 1%, by weight of the total weight of the spontaneously dispersible pharmaceutical 25 composition. The spontaneously dispersible pharmaceutical composition may also include sweetening or flavoring agents in an amount of up to about 2.5 or 5% by weight based on the total weight of the composition.

Thus in yet another aspect, the present invention provides a spontaneously dispersible 30 pharmaceutical composition for oral administration comprising
(a) up to 20% by weight of N-benzoyl-staurosporine,

- (b) 5 to 50% by weight of a hydrophilic component,
- (c) 5 to 80% by weight of a surfactant or surfactant mixture,
- (d) 5 to 85% by weight of a lipophilic component, and
- (e) 0.05 to 5 % by weight of an additive.

5

Naturally, any pharmaceutical composition of the present invention as described above in form of a micellar precursor can itself, i.e. before dilution with an aqueous medium, or after dilution with an aqueous medium, be present in the form of a an aqueous micellar solution (possibly comprising nanoparticles), an oily or aqueous emulsion, preferably a 10 microemulsion, and accordingly exhibit the structural features characteristic of such systems.

The pharmaceutical formulations, e.g. those in the examples hereinafter, may show good stability characteristics as indicated by standard stability trials, for example having a shelf 15 life stability of up to one, two or three years, and even longer. The pharmaceutical formulations of this invention produce aqueous microemulsions or aqueous micelles which are stable for up to one day or longer.

The pharmaceutical compositions of the invention exhibit especially advantageous 20 properties when administered orally. For example in terms of reduced variability and high level of bioavailability, e.g. obtained in standard bioavailability trials, e.g. by measuring the area under the plasma concentration(AUC)-time curve from e.g. 0 to 48 h, in units of mass-time/volume and C_{max} average, defined as highest observed concentration in plasma in units mass/volume. Such biopharmaceutical properties of the compositions of the invention, e.g. 25 the compositions of the Examples, may be determined in conventional manner, e.g. in standard animal tests, e.g. in rats or dogs, e.g. beagle dogs, or clinical trials. Typically, fasted beagle dogs, e.g. in groups of up to 8, e.g. 6 to 8, may be used and blood drug levels detected, e.g. using an HPLC method with fluorescence detection or e.g. by ELISA using a specific monoclonal antibody. Typically a dose of e.g. 25 mg or 50 mg, e.g. 50 mg, of 30 active agent may be administered. For example, typical AUC/dose values in $(h \cdot nmol/L)/(mg/kg)$ range from 960 to 1700 for Formulation A, from 380 to 1760 for Formulation B, and from 840 to 1970 for Formulation C. Typical C_{max} /dose values in

(nmol/L)/(mg/kg) range from 130 to 310 for Formulation A, from 60 to 280 for Formulation B, and from 140 to 310 for Formulation C.

In one aspect the invention provides a pharmaceutical composition for oral administration
5 comprising N-benzoylstaurosporine having an AUC(0-48h)/dose value (in
(h•nmol/L)/(mg/kg)) upon administration of a dose (in mg/kg) to fasted beagle dogs of up
to 2000, e.g. from 380 to 2000, e.g. from 840 to 2000.

In another aspect the invention provides a pharmaceutical composition for oral
10 administration comprising N-benzoylstaurosporine having a C_{max} /dose value (in
(nmol/L)/(mg/kg)) upon administration of a dose (in mg/kg) to fasted beagle dogs of up to
310, e.g. from 60 to 310, e.g. from 140 to 310.

Pharmacokinetic parameters, for example absorption and blood levels, also become
15 surprisingly more predictable and problems in administration with erratic absorption may be
eliminated or reduced. It has been found that the compositions of this invention reduce
variability in inter- and intra-patient dose response. Typically, the variability of
bioavailability is about 10 % for Formulation A, about 17 % for Formulation B, and about
14 % for Formulation C.

20 In another aspect the invention provides a pharmaceutical composition for oral
administration comprising N-benzoylstaurosporine and having a variability of bioavailability
of N-benzoylstaurosporine of less than 20%, e.g. from 5 % to 17 %, e.g. from 10 % to 17
%.

25 In another aspect the invention provides a method of increasing bioavailability or reducing
variability of bioavailability levels of N-benzoylstaurosporine, said method comprising orally
administering a composition of the invention to fasted beagle dogs, e.g. wherein N-
benzoylstaurosporine has an AUC(0-48h)/dose value (in (h•nmol/L)/(mg/kg)) upon
30 administration of a dose (in mg/kg) to fasted beagle dogs of up to 2000, e.g. from 380 to
2000, e.g. from 840 to 2000.

In another aspect the invention provides a method of increasing bioavailability or reducing variability of bioavailability levels of N-benzoylstaurosporine, said method comprising orally administering a composition of the invention to fasted beagle dogs, e.g. wherein N-5 benzoylstaurosporine has a $C_{max}/dose$ value (in (nmol/L)/(mg/kg)) upon administration of a dose (in mg/kg) to fasted beagle dogs of up to 310, e.g. from 60 to 310, e.g. from 140 to 310.

In another aspect the invention provides a method of increasing bioavailability or reducing variability of bioavailability levels of N-benzoylstaurosporine, said method comprising orally administering a composition of the invention to fasted beagle dogs, e.g. wherein the variability of bioavailability is less than 20%, e.g. from 5 % to 17 %, e.g. from 10 % to 17 %.

15 Additionally the pharmaceutical compositions of the present invention are effective with tenside materials, for example bile salts, being present in the gastro-intestinal tract. That is, the pharmaceutical compositions of the present invention are spontaneously dispersible in aqueous systems comprising such natural tensides and thus capable of providing aqueous microemulsion or aqueous micellar systems *in situ* which are stable. The function of the 20 pharmaceutical compositions in the present invention upon oral administration remain substantially independent of and/or unimpaired by the relative presence or absence of bile salts at any particular time or for any given individual.

In another aspect, the invention provides a process for the production of a spontaneously 25 dispersible pharmaceutical composition as defined above, which process comprises bringing the hydrophilic component and the surfactant (and additional components if required) into intimate admixture, and adding the active agent, i.e. N-benzoyl-staurosporine. When required, the composition may be compounded into unit dosage form, for example by encapsulation into soft or hard gelatine capsules. Optionally further components or 30 additives, in particular a hydrophilic co-component, for example ethanol, may be mixed with the two components or with or after addition of the active agent. For example, while the use of ethanol in the compositions is not essential, ethanol may provide additional

benefits, for example it has been found to be of particular advantage when the compositions are to be manufactured in soft gelatine, encapsulated form. This is because storage characteristics are improved, in particular the risk of active agent precipitation following encapsulation procedures is reduced. Thus the shelf life stability may be extended by

5 employing ethanol or some other such co-component as an additional ingredient of the hydrophilic component.

The utility of all the pharmaceutical compositions of the present invention may be observed in standard clinical tests in, for example, known indications of active agent dosages giving

10 equivalent blood levels of active agent; for example using dosages in the range from 25 mg to 300 mg, preferably from 100 to 225 mg, e.g. 120 to 225 mg, e.g. 150 mg of active agent per day for a 75 kilogram mammal, e.g. an adult human, and in standard animal models. The pharmaceutical profile, e.g. increased bioavailability and reduced variability of bioavailability, of the active agent provided by the compositions may be observed in

15 standard animal tests and in clinical trials, e.g. as described above.

In another aspect, the invention provides a method of increasing bioavailability levels or reducing variability of bioavailability levels of N-benzoylstaurosporine for patients during N-benzoylstaurosporine therapy, said method comprising orally administering a

20 composition of the invention.

In yet another aspect, the invention provides a use of N-benzoylstaurosporine in the manufacture of a medicament suitable for oral administration and having e.g. high bioavailability levels and a reduced variability of bioavailability of N-benzoylstaurosporine.

25

In yet another aspect, the invention provides a use of N-benzoylstaurosporine in the manufacture of a medicament having high bioavailability levels and a reduced variability of bioavailability of N-benzoylstaurosporine.

30 The pharmaceutical compositions of the present invention are preferably compounded in unit dosage form, for example by filling them into orally administrable capsule shells. The capsule shells may be soft or hard gelatine capsule shells. Where the pharmaceutical

composition of the present invention is in unit dosage form, each unit dosage will suitably contain from 25 to 100 mg active agent, preferably between 25 and 75 mg of the active agent, for example 25 or 50 mg. Such unit dosage forms are suitable for administration 1 to 5 times daily depending upon the particular purpose of therapy, the component of therapy and the like. However, if desired, the pharmaceutical compositions of the present invention may be in drink solution form and may include water or any other aqueous system, to provide formulations suitable for drinking.

The pharmaceutical compositions of the present invention are particularly useful for treatment and prevention of the conditions disclosed in US 5,093,330, the contents of which are incorporated herein by reference. Most notably, these compositions show high anti-proliferative and anti-tumor activity, as a result of Protein Kinase C (PKC) inhibition, which may be extremely useful for cancer treatment. Moreover, their highly selective and potent inhibition of PKC may lead to superior clinical outcomes for the patient (i.e. delay or suppress disease progression) with equally tolerable regimens. Potential applications include a variety of solid tumors and more specifically for example breast cancer, colon cancer, ovarian cancer and leukemia. In addition, various other indications that may be affected by PKC activity may be effectively treated by these compositions, including Multidrug Resistance (MDR), one of the major problems in currently employed cancer chemotherapy, and inflammatory diseases in general.

Thus, in another aspect the present invention provides a method of treatment comprising administering a dispersible pharmaceutical composition according to the present invention to a subject in need of such treatment.

25

Following is a description by way of example only of compositions of this invention and are not intended to limit the scope of the present invention.

Examples 1 to 4

Particulate measurements, including mean size measurement of dispersed particles (diameter), measured at a 90° scattering angle and a temperature 20°C, were performed using a Malvern Zetasizer 3000. The carrier was prepared by mixing the components one with another. The 5 active agent N-benzoyl-staurosporine is then dissolved in the carrier by stirring. No phase separation or precipitation is observed for any of the described compositions 1 to 4 which are and remain clear.

Table 1: Composition of Formulations 1 to 4

		<i>I</i>	<i>II</i>	<i>III</i>	<i>IV</i>
<i>Co-/Surfactants</i> %(g/g)	Cremophor RH 40	42.750	66.500	57.000	
	Solutol HS 15				75.905
	Labrafil M2125 CS		18.905		
<i>Hydrophilic</i> <i>Component</i> %(g/g)	PEG 400	25.65			
	Propylene Glycol		9.500	4.750	9.500
	Ethanol abs.	9.500			9.500
	Triethylcitrate			4.750	
<i>Lypophilic</i> <i>Component</i> %(g/g)	Corn Oil Glycerides	17.005		28.405	
<i>Other Additives</i> %(g/g)	Tocopherol	0.095	0.095	0.095	0.095
<i>Active Agent</i> %(g/g)		5.000	5.000	5.000	5.000
<i>Total</i>			100.0	100.0	100.0
<i>Mean Particle Size</i> (nm)		31.6	20.4	66.3	157.3

Example 5

Pharmacokinetic parameters and plasma profiles of N-benzoylstaurosporine administered in the following threee formulations A, B and C (filled into hard gelatin capsules) were analyzed:

- A microemulsion preconcentrate containing Cremophor and PEG,
- B microemulsion preconcentrate containing Cremophor and Labrafil,
- C microemulsion preconcentrate containing Solutol.

Using a two-block latin square design, two hard gelatin capsules of each formulation A, B or C containing N-benzoyl-staurosporine were deposited deeply into the throat of each of eight male Beagle dogs (3 to 5 years, 10 to 14 kg). A subsequent rinse of the throat was performed, using 20 mL of demineralized water to be swallowed. The nominal dose of 50 mg applied per animal corresponds to actual doses between 3.5 and 4.9 mg/kg body weight (see Table 2).

The dogs were fasted for at least 15 h prior to administration, but had free access to tap water throughout the experiment. Around 6 h (range 6.0-6.3) after oral administration, each animal received around 350 g pellets. Blood (3 mL) was collected from the Vena cephalica into 5 mL polystyrene tubes containing Li-heparin as anticoagulant (at least 15 I.U. heparin per mL blood), at the following time points: 0 (= before) and 0.17, 0.5, 0.75, 1, 1.5, 2, 4, 6, 8, 12, 24, 30, 36, and 48 hours post dose. The heparinized blood samples were centrifuged (about 2150 g, 10 min, about 4 °C), not longer than 30 min post withdrawal, and the supernatant plasma was collected into plain polystyrene tubes colored dark brown to avoid further daylight exposure. The plasma samples were frozen and stored below -18°C pending analysis.

Concentrations of N-benzoyl-staurosporine in plasma were determined by an HPLC method with fluorescence detection.

The pharmacokinetic parameters C_{max} (highest observed concentration in plasma); t_{max} (time to reach C_{max}); and $AUC(0-48h)$ (area under the plasma concentration-time curve from 0 to 48 h, calculated by the linear trapezoidal rule, wherein concentrations below the limit of quantitation (LOQ) were taken as 'zero'), are listed in Table 2. Individual and mean (N=6*) plasma concentrations of N-benzoyl-staurosporine in dogs 1 to 8 after oral administration of single doses of 50 mg as formulation A, B, or C are shown in Figures 1, 2, and 3, respectively (wherein T stands for time after dosing, and M stands for the mean concentration).

Dogs No. 2 and No. 6 were excluded from means calculation as it was questionable whether they properly ingested the appropriate dosages.

Table 2: Pharmacokinetic parameters

Individual and mean (N=6*) pharmacokinetic parameters derived from the plasma concentrations of N-benzoyl-staurosporine in eight dogs after administration of single doses of 50 mg[†] N-benzoyl-staurosporine in form of three different formulations.

Formulation	Parameter	Units	Animal no.	Mean				SEM	N
				1	2*	3	4		
A	Dose	mg/kg	4.796	4.155	3.736	3.708	4.590	4.304	3.394
	C _{max}	nmol/L	633	954	1160	621	1148	816	633
	C _{max} /dose [‡]	(nmol/L)/(mg/kg)	132	230	310	167	250	190	187
	t _{max}	h	2	2	1	2	2	2	2 [†]
	AUC(0-48h)	h·nmol/L	4958	7944	5627	3565	7872	6232	3827
	AUC(0-48h)/dose [‡]	(h·nmol/L)/(mg/kg)	1034	1912	1506	961	1715	1448	1128
B	Dose	mg/kg	4.809	4.157	3.773	3.847	4.809	4.379	3.504
	C _{max}	nmol/L	299	1153	1079	486	792	617	593
	C _{max} /dose [‡]	(nmol/L)/(mg/kg)	62	277	286	126	165	141	169
	t _{max}	h	1.5	2	2	4	2	2	2 [†]
	AUC(0-48h)	h·nmol/L	1840	8769	6642	3465	6496	5280	4531
	AUC(0-48h)/dose [‡]	(h·nmol/L)/(mg/kg)	383	2110	1760	901	1351	1206	1293
C	Dose	mg/kg	4.733	4.176	3.883	3.681	4.897	4.498	3.550
	C _{max}	nmol/L	799	503	1212	686	1078	719	506
	C _{max} /dose [‡]	(nmol/L)/(mg/kg)	169	120	312	186	220	160	143
	t _{max}	h	2	2	2	2	4	2	1.5
	AUC(0-48h)	h·nmol/L	4890	3657	7674	3881	6528	5472	3671
	AUC(0-48h)/dose [‡]	(h·nmol/L)/(mg/kg)	1033	876	1976	1054	1333	1217	1034

* either dog no. 2 got only 25 mg of B or dog no. 6 got only 25 mg of C, therefore, both were excluded from means calculation,

[†] median time to C_{max},

[‡] corrected for actual dose,

SEM standard error of the mean.

CLAIMS

1. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine.

5

2. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine in the form of a micellar precursor.

3. A spontaneously dispersible pharmaceutical composition for oral administration comprising

10

- 1) N-benzoyl-staurosporine,
- 2) a hydrophilic component, and
- 2) a surfactant.

15

4. A composition as claimed in any one of claims 1 to 3 comprising a lipophilic component.

5. A composition as claimed in any preceding claim wherein the hydrophilic component comprises 1,2-propylene glycol or a polyethylene glycol.

20

6. A composition as claimed in any preceding claim comprising ethanol as a hydrophilic co-component.

7. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and a surfactant selected from the group consisting of polyoxyethylenes, polyglycerols and related polyols, and polyalkylene oxide copolymers.

25

8. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and a surfactant selected from the group consisting of a polyoxyethylene castor oil, a polyoxyethylene alkyl ether, and a polysorbate.

9. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and a surfactant having a HLB value of greater than 10 and a co-surfactant having a HLB value of less than 10.

5

10. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and surfactant selected from the group consisting of a polyoxyethylene castor oil, a polyoxyethylene alkyl ether, and a polysorbate, and a transesterified ethoxylated vegetable oil as a co-surfactant.

10

11. A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and a surfactant having a HLB value of greater than 10 and fatty acid glyceride as a lipophilic component.

15 12.

A spontaneously dispersible pharmaceutical composition for oral administration comprising N-benzoyl-staurosporine, and surfactant selected from the group consisting of a polyoxyethylene castor oil, a polyoxyethylene alkyl ether, and a polysorbate, and a lipophilic component selected from the group consisting of a fractionated coconut oil, a corn oil glyceride, and a acetylated mono- or diglyceride.

20

13. A spontaneously dispersible pharmaceutical composition for oral administration comprising

- (a) up to 20% by weight of N-benzoyl-staurosporine,
- (b) 5 to 50% by weight of a hydrophilic component,
- (c) 5 to 80% of a surfactant or surfactant mixture,
- (d) 5 to 85% of a lipophilic component, and
- (e) 0.05 to 5 % of an additive.

25

14. A method of treatment for treating subjects in need of N-benzoyl-staurosporine therapy comprising administering a dispersible pharmaceutical composition according to any preceding claim to a subject in need of such treatment.

30

15. A pharmaceutical composition for oral administration comprising N-benzoylstaurosporine and having (a) a reduced variability of bioavailability levels of N-benzoylstaurosporine or (b) a high bioavailability levels of N-benzoylstaurosporine.
16. A pharmaceutical composition for oral administration comprising N-benzoylstaurosporine and having
 - (a) a variability of bioavailability levels of N-benzoylstaurosporine of from 5 to 17%
 - (b) an AUC(0-48h)/dose value (in (h•nmol/L)/(mg/kg)) of from 380 to 2000, or
 - (c) a C_{max} /dose value (in (nmol/L)/(mg/kg)) of from 60 to 310,
upon administration of a dose (in mg/kg) of N-benzoylstaurosporine to fasted beagle dogs.
17. A method of increasing bioavailability levels or reducing variability of bioavailability levels of N-benzoylstaurosporine by mixing N-benzoylstaurosporine with a carrier comprising a hydrophilic component, and a surfactant.
18. A method of increasing bioavailability levels or reducing variability of bioavailability levels of N-benzoylstaurosporine, said method comprising orally administering a composition according to any preceding claim to fasted beagle dogs.
19. A method according to claims 17 or 18 wherein N-benzoylstaurosporine has
 - (a) a variability of bioavailability levels of from 5 to 17 %,
 - (b) an AUC(0-48h)/dose value (in (h•nmol/L)/(mg/kg)) of from 380 to 2000, or
 - (c) an C_{max} /dose value (in (nmol/L)/(mg/kg)) of from 60 to 310,
upon administration of a dose (in mg/kg) of N-benzoylstaurosporine to fasted beagle dogs.
20. A method of increasing bioavailability levels or reducing variability of bioavailability levels of N-benzoylstaurosporine for patients during N-benzoylstaurosporine therapy, said method comprising orally administering a composition according to

any preceding claim.

21. Use of N-benzoylstaurosporine in the manufacture of a medicament suitable for oral administration.

5

22. Use of N-benzoylstaurosporine in the manufacture of a medicament having high bioavailability levels or a reduced variability of bioavailability of N-benzoylstaurosporine.

10 23. A composition substantially as hereinbefore described with reference to the Examples.

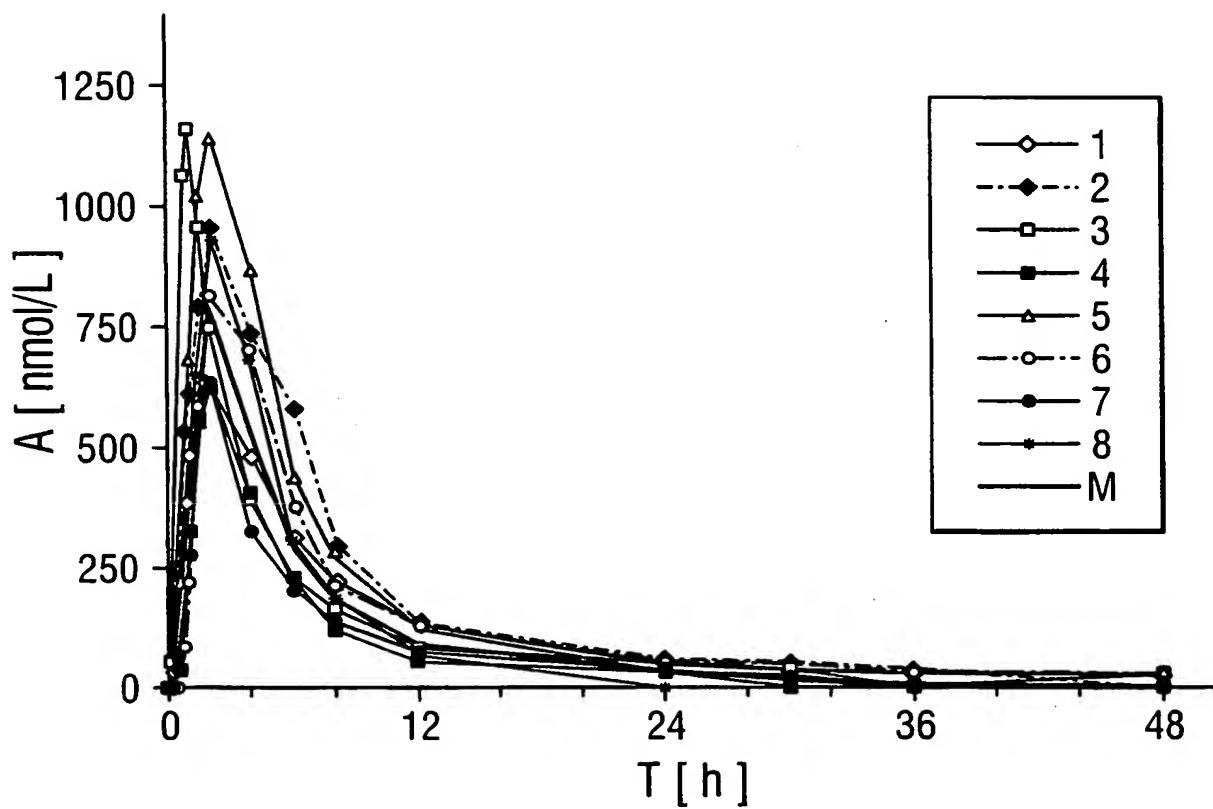


Fig. 1

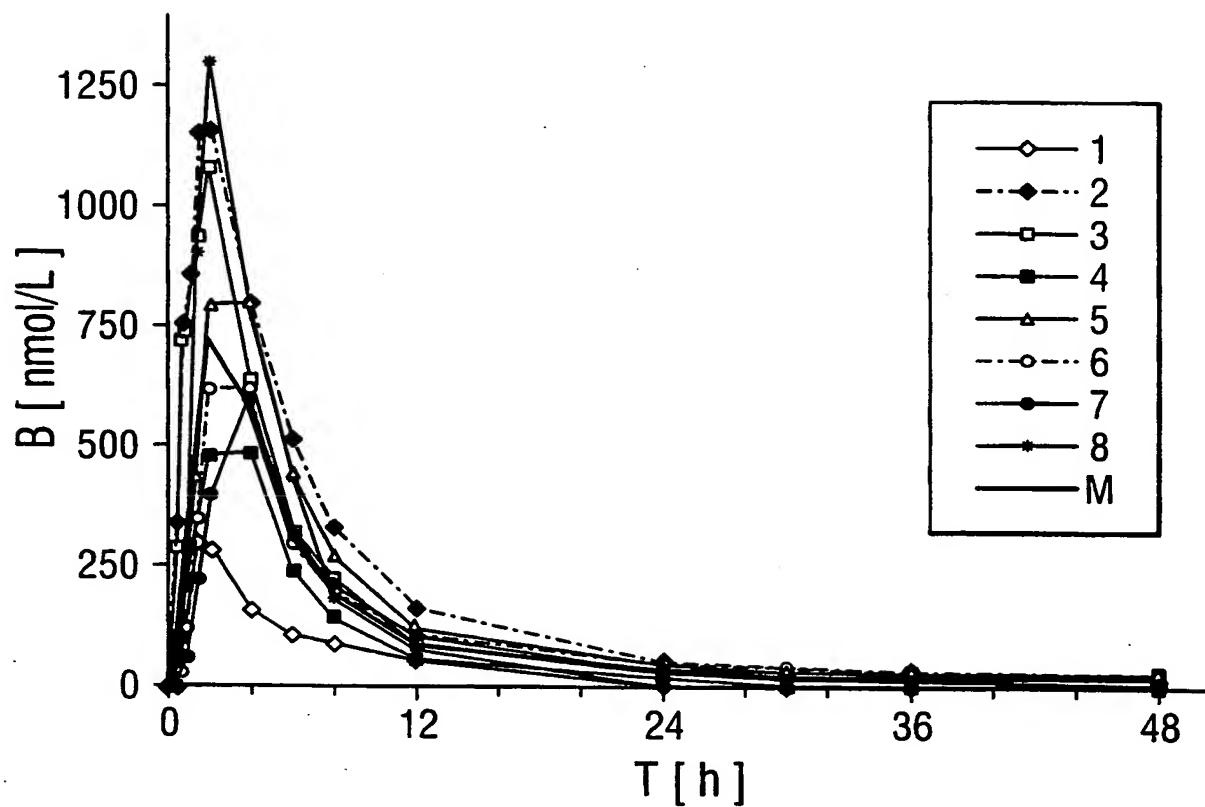


Fig. 2

3 / 3

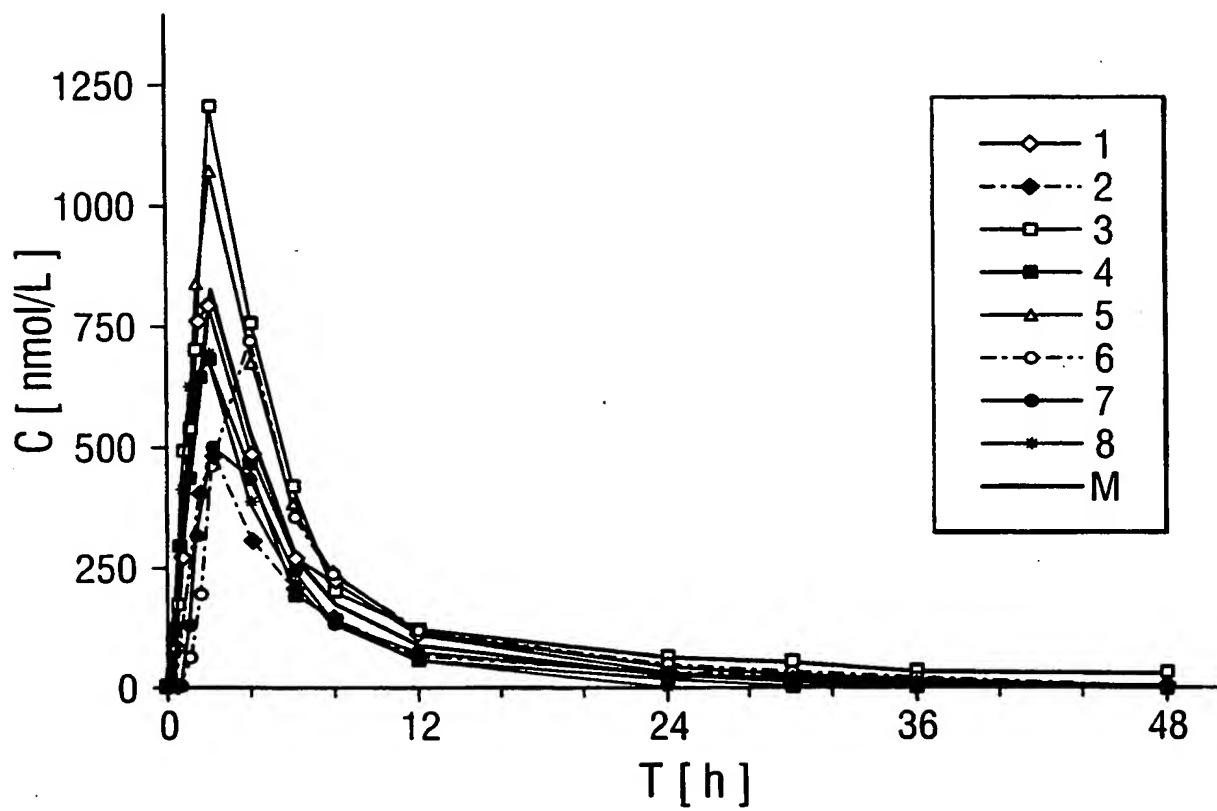


Fig. 3

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/EP 00/01196

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/107 A61K31/553

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 657 164 A (CIBA-GEIGY AG) 14 June 1995 (1995-06-14) the whole document	21
Y	---	1-20, 22, 23
X	EP 0 733 358 A (CIBA-GEIGY AG) 25 September 1996 (1996-09-25) claims 1-5 page 5, column 7, line 40 - line 52	1, 3, 6, 7, 17
X	EP 0 711 556 A (CIBA-GEIGY AG) 15 May 1996 (1996-05-15) claims 1, 2 page 5, line 48 - line 52	1-4, 7, 8, 11, 12, 17
	---	-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

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- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search

14 June 2000

Date of mailing of the international search report

21/06/2000

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/01196

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 33512 A (NOVARTIS AG ET AL.) 6 August 1998 (1998-08-06) claims 1-3,7-11 page 6, line 28 -page 7, line 16 -----	1-3, 5-10, 14-20, 22,23
Y	DE 44 18 115 A (SANDOZ-PATENT-GMBH) 1 December 1994 (1994-12-01) claims 1-9 -----	1,4, 11-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/01196

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 657164	A 14-06-1995	AT 185970	T	15-11-1999
		AU 692801	B	18-06-1998
		AU 8030894	A	22-06-1995
		CA 2137764	A	12-06-1995
		DE 69421366	D	02-12-1999
		DE 69421366	T	23-03-2000
		ES 2140512	T	01-03-2000
		IL 111872	A	08-02-1998
		JP 7196512	A	01-08-1995
		NZ 270109	A	26-11-1996
		US 5736542	A	07-04-1998
		ZA 9409824	A	13-07-1995
EP 733358	A 25-09-1996	AU 4809496	A	03-10-1996
		AU 4809596	A	03-10-1996
		CA 2172110	A	22-09-1996
		CA 2172111	A	22-09-1996
		EP 0733372	A	25-09-1996
		HU 9600700	A	28-02-1997
		HU 9600701	A	28-02-1997
		JP 8268915	A	15-10-1996
		JP 8268893	A	15-10-1996
		NO 961136	A	23-09-1996
		NO 961137	A	23-09-1996
		NZ 286206	A	26-05-1997
		NZ 286207	A	24-04-1997
		US 5726164	A	10-03-1998
		ZA 9602248	A	23-09-1996
		ZA 9602249	A	23-09-1996
EP 711556	A 15-05-1996	AU 3661695	A	23-05-1996
		AU 3661795	A	23-05-1996
		CA 2162341	A	10-05-1996
		CA 2162342	A	10-05-1996
		EP 0711557	A	15-05-1996
		FI 955311	A	10-05-1996
		FI 955312	A	10-05-1996
		HU 78026	A	28-05-1999
		HU 74423	A	30-12-1996
		JP 8208486	A	13-08-1996
		JP 8208522	A	13-08-1996
		NO 954485	A	10-05-1996
		NO 954486	A	10-05-1996
		NZ 280419	A	24-04-1997
		NZ 280420	A	24-03-1997
		US 5658898	A	19-08-1997
		ZA 9509457	A	09-05-1996
		ZA 9509458	A	20-06-1996
WO 9833512	A 06-08-1998	AU 6214198	A	25-08-1998
		BR 9807528	A	14-03-2000
		CN 1246058	T	01-03-2000
		CZ 9902663	A	13-10-1999
		DE 19882037	T	16-12-1999
		EP 0988046	A	29-03-2000
		GB 2335854	A	06-10-1999
		PL 334850	A	27-03-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members			International Application No PCT/EP 00/01196	
Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
DE 4418115	A 01-12-1994	BE 1008329 A CA 2124259 A CH 686761 A ES 2098180 A FR 2705566 A GB 2278780 A, B IT 1272992 B JP 11315022 A JP 7138161 A US 5932243 A GB 2315216 A, B	02-04-1996 28-11-1994 28-06-1996 16-04-1997 02-12-1994 14-12-1994 01-07-1997 16-11-1999 30-05-1995 03-08-1999 28-01-1998	

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